

**USE-DEPENDENT VENTRICULAR CONDUCTION SLOWING BY A VARIETY OF ANTIARRHYTHMIC DRUGS IN MAN.**

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Electrophysiological studies (EPS) have demonstrated qualitative frequency-dependent effects of antiarrhythmic agents (AA) in man but quantitative analysis of their kinetics of action has been limited. The purpose of this study was to determine in man the kinetics of a number of AA with differing rate-dependent properties *in vitro*. Twenty-three pts were studied during EPS while receiving flecainide (F, 8 pts), propafenone (P, 4 pts), quinidine (Q, 6 pts), amiodarone (A, 4 pts) or encainide (E, 1 pt). Rate-dependent effects of AA on QRS duration were determined after the onset of right ventricular pacing at a cycle length of 400 msec.

**Results:** In the absence of AA, no rate-dependent changes in QRS duration were found. All drugs increased QRS duration with an exponential time course, after the onset of pacing. The time constant of rate-dependent QRS prolongation averaged  $26 \pm 10$  beats ( $\text{mean} \pm \text{SD}$ ) for F,  $15 \pm 2$  for P,  $7 \pm 2$  for Q,  $4 \pm 2$  for A and 32 for E. These values are similar to the mean time constant in the literature for the onset of block of  $V_{\text{max}}$ , which are: 34 beats (F), 12 (P), 4-6 (Q), 2-3 (A) and 40 (E).

**We conclude** that AA produce use-dependent ventricular conduction slowing in man with a time dependence specific for each drug and similar to the reported time course of changes in  $V_{\text{max}}$  *in vitro*. This study confirms the relevance of experimental observations about use-dependent AA action for understanding AA effects in man.

**COMPARATIVE EFFECTS OF INTRAVENOUS VERAPAMIL AND PROPRANOLOL ON INDUCIBILITY CATECHOLAMINE-SENSITIVE ATRIOVENTRICULAR RECIPROCATING TACHYCARDIA.**

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To compare efficacy of intravenous verapamil with intravenous propranolol in suppressing inducibility of catecholamine-sensitive atrioventricular (AV) reciprocating tachycardia (RT), we studied 17 pts in whom induction of AV RT depended on intravenous infusion of isoproterenol (2-8  $\mu\text{g}/\text{min}$ ). In all pts, AV RT used AV node-His Purkinje system for antegrade and anomalous pathway (AP) for retrograde conduction. Seven pts (group I) received intravenous verapamil (0.15 mg/kg followed by 0.005 mg/kg/min) and 10 pts (group II) received intravenous propranolol (0.15 mg/kg). Verapamil suppressed inducibility of AV RT in only 2/7 (28%) group I pts despite terminating AV RT in 4/7 pts; verapamil depressed AV node conduction but exerted no effects on AP. In contrast, propranolol completely abolished inducibility of AV RT in 10/10 (100%) group II pts by reversing isoproterenol-induced facilitation of conduction in atrium, AV node, ventricle and AP. Furthermore, propranolol blocked retrograde AP conduction in 2/10 group II pts and slowed ventricular rate by 45% in 3 group II pts with inducible atrial fibrillation with ventricular preexcitation. Thus, in pts with catecholamine-sensitive AV RT, propranolol is far more specific and effective than verapamil in suppressing inducibility of AV RT, and beta-adrenergic blockade should be considered treatment of choice for chronic prophylaxis.

**TERMINATION OF ATRIAL FLUTTER BY PROCAINAMIDE AND FLECAINIDE IN THE PORCINE HEART.**

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Procainamide (P, n=6) or flecainide (F, n=10) were used to terminate atrial flutter (AF) in a reentry model with a partially refractory excitable gap. Plunge wire electrodes were introduced around a Y-shaped incision in the right atrium in 16 pigs (body weight approx. 32 kg), and 59 sustained AF's (mean cycle length  $171 \pm 15$  ms) were induced by programmed stimulation in 14 pigs. Strength-interval curves were obtained with 2 ms stimuli to assess excitability. P or F were administered until the termination of AF. Flutter cycle length increased gradually to  $269 \pm 74$  ms after F and to  $281 \pm 33$  ms after P (not different, P versus F). Current thresholds, refractory periods (RP) and conduction velocity at baseline and at termination were:

	baseline	procainamide	baseline	flecainide
Thresh. (mA)	$1.3 \pm 0.8$	$1.4 \pm 0.4$	$0.7 \pm 0.4$	$1.2 \pm 0.6^*$
Effec. RP(ms)	$198 \pm 15$	$228 \pm 16^*$	$205 \pm 22$	$201 \pm 24$
Absol. RP(ms)	$155 \pm 18$	$184 \pm 16^*$	$158 \pm 21$	$164 \pm 22$
Cond. (cm/s)	$50 \pm 7$	$30 \pm 4^*$	$45 \pm 2$	$28 \pm 4^*$

Mean values  $\pm$  SD; \* =  $p < 0.05$  versus corresponding baseline value.

In conclusion, both drugs terminate this subtype of reentry by a comparable reduction of the conduction velocity, procainamide by its effect on atrial refractoriness and flecainide by an increase of the current threshold and hence by its inhibition of the source of propagation. Therefore, this model differentiates class Ia (procainamide) from class Ic (flecainide) antiarrhythmic activities.

**MEXILETINE-THEOPHYLLINE INTERACTION**

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Recent case reports suggest that the antiarrhythmic agent, mexiletine, raises plasma levels of methylxanthines, potentially increasing theophylline toxicity. The present study evaluated mexiletine effects on steady state theophylline levels in 8 healthy men. Theophylline (Theo-Dur, 300 mg) tablets were given each 12 hr for 9 days. By day 2 mean pre-dose (trough) plasma theophylline had stabilized between 6.0 and 7.3  $\text{mg} \cdot \text{L}^{-1}$ . Mexiletine, 200 mg each 8 hr was added on days 6 and 7, causing a 70% elevation in trough theophylline levels, which promptly returned to prior levels when this antiarrhythmic was withdrawn. Mexiletine levels remained within the therapeutic range ( $\leq 1.4 \text{ mg} \cdot \text{L}^{-1}$ ) and no arrhythmias occurred.

	Before Mexiletine	With Mexiletine
Mean plasma theo ( $\text{mg} \cdot \text{L}^{-1}$ )	$8.1 \pm 0.1$	$13.4 \pm 0.6^*$
AUC <sub>0-12</sub> ( $\text{mg} \cdot \text{L}^{-1} \cdot \text{hr}$ )	$96.8 \pm 9.1$	$160.2 \pm 3.7^*$
Theo clearance ( $\text{mL} \cdot \text{hr}^{-1}$ )	$44.7 \pm 5.1$	$25.4 \pm 1.2^*$

\* $p < 0.01$

These data indicate that mexiletine elevates plasma levels of concomitantly administered theophylline. Plasma theophylline levels should be monitored and its dosage reduced when mexiletine is added.